Kidney International, Vol. 36 (1989), pp. 730–740

NEPHROLOGY FORUM

Nephrotoxicity of contrast media

Principal discussant: ARNOLD S. BERNS

Michael Reese Hospital and University of Chicago, Chicago, Illinois

Case presentation

A 64-year-old man was admitted to the hospital for evaluation of progressive dyspnea and increasing angina. The medical history was significant for coronary artery disease with an uncomplicated myocardial infarction 8 years ago. Diabetes was diagnosed 10 years ago and was controlled currently with diet alone. Peripheral vascular disease necessitated a left below-the-knee amputation 2 years ago. Although previously a "heavy" smoker, he had stopped smoking 5 years ago. Current medications included furosemide, persantine, and digoxin.

Physical examination revealed a blood pressure of 120/76 mm Hg; pulse, 82 beats/min and regular; and respirations, 24/min. No jugular venous distension was present. The chest had bibasilar rales. Cardiac examination was unremarkable. There was no abdominal organomegaly. External genitalia and rectal examination were unremarkable. A sensory-motor peripheral neuropathy was present.

Laboratory data on admission included: sodium, 138 mEq/liter; potassium, 5.5 mEq/liter; chloride, 109 mEq/liter; and carbon dioxide, 22 mEq/liter. The BUN was 68 mg/dl and the creatinine 3.8 mg/dl. Glucose was 123 mg/dl. Urinalysis revealed 3+ albumin, trace glucose, 6–9 white blood cells/high-power field, and no casts. An electrocardiogram showed normal sinus rhythm and evidence of an old, anteroseptal myocardial infarction. A plain chest film disclosed small bilateral pleural effusions and changes of chronic obstructive pulmonary disease. Renal ultrasound examination was normal. The 24-hour creatinine clearance was 26 ml/min. Urine protein excretion was 5.8 g/24 hours.

The patient was scheduled for coronary angiography. Prior to angiography he received 1000 ml of 0.45% saline over 10 hours, which was followed by 200 ml of 20% mannitol over 3 hours. Iopamidol (Isovue, Squibb), 140 cc, was administered, and furosemide, 40 mg, was given intravenously immediately upon completion of the angiographic procedure. The procedure revealed severe proximal stenosis of the left anterior descending and circumflex coronary arteries. A dominant right coronary artery had only a mild proximal stenosis.

In the 24 hours after angiography, his urine output was 1800 cc. Intravenous 0.45% saline was administered to replace urinary losses. On the first day after the angiogram, the creatinine was 5.5 mg/dl. Oliguria did not occur, but the serum creatinine rose to 6.4 mg/dl on the second day. Over the next several days, the serum creatinine concentration gradually fell, and 6 days after the angiogram it was 3.5 mg/dl.

Eight days after having the angiogram, the patient was scheduled for percutaneous transluminal coronary angioplasty (PTCA). Intravenous 0.45% saline and mannitol were given again according to the previous protocol, and 360 cc of iopamidol was administered. Within 24 hours of successful two-vessel PTCA, the patient became oliguric. Furosemide, metolazone, and low-dose dopamine, 2 μg/kg/min, were administered without response. On the first day following the angioplasty, the creatinine rose to 6.9 mg/dl. Six days after angioplasty, the creatinine peaked at 8.3 mg/dl. On the seventh day, urine output abruptly rose to 3000 cc/24 hours, and the serum creatinine began to fall. Two weeks after angioplasty, the patient was discharged with a stable serum creatinine of 4.0 mg/dl.

Discussion

DR. ARNOLD S. BERNS (*Attending Physician, Michael Reese Hospital and Medical Center, and Assistant Clinical Professor of Medicine, Pritzker School of Medicine, University of Chicago, Chicago, Illinois*): In the modern era of invasive diagnostic and therapeutic medicine, we now recognize contrast-associated nephropathy as an important cause of renal failure. Indeed, one recent review of hospital-acquired acute renal failure documented that radiocontrast agents accounted for 12% of episodes of renal failure and that these agents exceeded aminoglycoside antibiotics in nephrotoxic potential [1]. Early studies reported sporadic cases of oliguric renal failure following the administration of di-iodinated contrast material used for either excretory urography or aortography [2–7]. These reports prompted some authors to suggest that procedures requiring contrast media should be prohibited in patients with preexisting renal insufficiency. But tri-iodinated compounds with greater water solubility became available, and several studies demonstrated the safety of these agents (at least in the relatively low dosages employed) and endorsed their use, even for patients with advanced renal insufficiency [8, 9]. With the expanding use of synthetic, tri-iodinated compounds—for the most part the sodium or meglumine salts of diatrizoate—well-documented case reports of both reversible and irreversible acute renal failure following excretory urography, drip-infusion urography, and arteriography began to appear [10–15].

Presentation of this Forum is made possible by grants from Pfizer, Incorporated; Merck Sharp & Dohme; Sandoz, Incorporated; E. R. Squibb & Sons, Incorporated; and the CIBA-GEIGY Corp.

As I review the subject of contrast-associated nephrotoxicity, I will refer to the patient we are discussing today. He illustrates many of the important clinical issues and dilemmas that confront clinicians caring for patients undergoing contrast-dependent diagnostic and therapeutic procedures. In this Forum, I will review the clinical aspects of contrast-associated nephrotoxicity, emphasizing its recognition as a characteristic syndrome that occurs in high-risk patients. I will review the literature pertaining to the pathophysiology of this syndrome and to recently described animal models of contrast nephrotoxicity. Finally, I will summarize data on the use of the newer nonionic contrast agents and their comparative renal toxicity.

Epidemiology and clinical course

The literature on contrast-associated nephrotoxicity does not reveal the true incidence of the syndrome. Several large retrospective studies attest to the relatively low incidence of contrast-associated nephrotoxicity following excretory urography, however. One large retrospective review from the Mayo Clinic reports no cases of renal failure following excretory urography in more than 100,000 studies in nondiabetic patients. Among diabetic patients, the incidence of renal failure was 0.2% [16]. Another large retrospective study, also from the Mayo Clinic, analyzed the incidence of acute renal failure following aortography in 7400 patients; of this group, 8 patients (0.11%) were referred to nephrologists because of renal failure [17]. Five of these patients had an elevated baseline creatinine concentration ranging from 1.4 to 2.2 mg/dl. Additional retrospective studies report the incidence of contrast-associated renal toxicity to be less than 1% following either intravenous pyelography or major arteriography, including cerebral, aortic, and peripheral arteriography [14, 18, 19].

On the other hand, several prospective studies document a higher incidence of contrast-related renal impairment ranging from 3.7% to 70% [19–23]. In 12 additional reports, an aggregate incidence of 10.2% (204/1999) was documented following intravenous pyelography and major arteriography [24–35].

What accounts for the variable incidence of nephrotoxicity among the published clinical reports? Several points are obvious, including the limitations of retrospective analysis, in which case detection is contingent on either documentation by nephrology consultation, or on the availability of renal-function data both before and after contrast administration. Clearly, such retrospective analysis tends systematically to underestimate the true incidence of contrast-associated nephrotoxicity. However, prospective studies also have yielded widely varying estimates of the incidence of contrast-associated nephrotoxicity, apparently because of differences in patient selection, state of hydration, rate and site of administration, dose of contrast agent, and variable definitions of acute renal failure.

In my opinion, the literature amply documents the relative safety of contrast media as used for intravenous pyelography, enhanced computerized tomography, and arteriography in the majority of patients. However, it appears that there is a subpopulation of patients who have a substantially greater likelihood of developing contrast-associated nephrotoxicity.

Several authors have tried to identify the factors that increase the risk of contrast-associated nephrotoxicity [14, 16, 18, 19, 21, 25, 36–39]. Table 1 shows the prevalence of such risk factors. Because many of these risk factors can coexist, it has not been possible to determine the independent contribution of each to the development of renal failure.

Table 1. Prevalence of risk factors in patients with contrast-associated nephrotoxicity[a]

Risk factors	% Prevalence
Azotemia, Cr ≥ 1.5 mg/dl	60
Albuminuria, >2+	56
Hypertension	55
Age, >60 yrs	51
Dehydration	41
Uric acid, >8.0 mg/dl	41
Multiple studies	29
Solitary kidney	13
Contrast medium, >2 ml/kg	11
Multiple myeloma	2

[a] Data compiled from Refs. 14, 16, 18, 19, 21, 25, 36–39.

Baseline renal insufficiency, usually defined as a serum creatinine of at least 1.5 mg/dl, predisposes to the development of further renal impairment following exposure to contrast medium. In a prospective study of 378 patients undergoing non-renal angiography, renal failure (defined as an acute increase in serum creatinine of ≥ 1.0 mg/dl) developed in only 2% of patients with a serum creatinine less than 1.5 mg/dl but in 30% of patients with a baseline serum creatinine of at least 1.5 mg/dl [20]. Similarly, in a prospective study of 124 patients undergoing intravenous urography, an at least 25% increase above baseline serum creatinine was seen in 15% of patients with an initial creatinine level of less than 2.0 mg/dl, but in 55% of those with an initial level of at least 2.0 mg/dl [22]. In 11 studies in which risk factors were tabulated [14, 16, 18, 20–22, 25, 36–39], 60% of patients who developed contrast-associated nephrotoxicity had pre-existing renal impairment (Table 1). Underlying renal disease is the most prevalent risk factor.

A more detailed analysis of risk factors was published recently [40]. In 1144 patients undergoing cardiac catheterization with iopamidol, a nonionic contrast agent, baseline renal insufficiency was the only confirmed predictor of contrast-associated nephropathy. At basal serum creatinine levels of 1.1 mg/dl or less, the probability of nephrotoxicity developing was approximately 4%. As basal serum creatinine levels rose, however, the risk rose exponentially; at levels greater than 2.0 mg/dl, the probability for developing nephrotoxicity (defined as an acute increase in creatinine of ≥ 0.5 mg/dl) exceeded 20%.

The second most important risk factor appears to be diabetes mellitus. Prospective as well as retrospective studies have concluded that diabetic patients are at increased risk of developing contrast-associated nephrotoxicity [14, 16, 23, 28, 30, 32, 37–39]; many of these studies, however, have focused on diabetic patients with far advanced renal disease.

How does exposure to radiocontrast media affect the diabetic patient who has normal or only midly impaired renal function? In a study of 49 non-dehydrated diabetic patients with serum creatinine levels of less than 2.0 mg/dl, only 3 (6%) experienced an increase in basal serum creatinine of at least 25% following the administration of intravenous contrast material [27]. In this study, the presence of proteinuria did not appear to predispose to renal toxicity. In another review of nonazotemic diabetics (serum creatinine ≤ 2.0 mg/dl), 4 of 24 patients (17%) undergoing intravenous pyelography developed renal failure, defined as

Table 2. Incidence of contrast-induced renal failure in diabetic patients[a]

Creatinine <2.0 mg/dl	11/306	3.6%
Creatinine 2.0–4.0 mg/dl	22/81	27.0%
Creatinine >4.0 mg/dl	30/37	81.0%

[a] Data from Refs. 19–22, 27, 28, 31, 32, 34, 35, 41.

an increase in serum creatinine of at least 0.2 mg/dl. Of the 16 patients in this group with serum creatinines of less than 1.5 mg/dl, only one developed contrast-associated nephrotoxicity [31]. A recently reported prospective study of 85 diabetic patients without renal insufficiency (mean serum creatinine of 1.0 mg/dl) failed to identify a single episode of renal failure following exposure to intravascular contrast medium [35].

Azotemic patients with diabetes appear to have a substantially higher incidence of acute renal failure following exposure to contrast medium than do nonazotemic patients with diabetes [28, 32, 34, 39]. As Table 2 shows, the literature also suggests that the incidence of renal failure increases at progressively higher values of baseline creatinine levels. Data also suggest that at any given level of azotemia, the diabetic patient is more likely to experience contrast-associated renal failure than is the nondiabetic [34, 35]. This hypothesis, however, has not been evaluated prospectively over large ranges of serum creatinine values. A recent prospective study found an 8.8% incidence of renal failure among azotemic diabetics (mean creatinine 2.97 ± .27 mg/dl), a 3.5% incidence in nondiabetics with similar degrees of mild renal insufficiency (mean creatinine 2.2 ± .05 mg/dl), and a 4.5% incidence in nondiabetics with more severe renal insufficiency (mean creatinine 4.08 ± .17 mg/dl) [35]. As I previously noted, none of the nonazotemic diabetics experienced renal failure.

Several other potentially important risk factors have been implicated. Among patients who develop contrast-associated renal failure, approximately 50% are older than 60 years. This finding might reflect an increased prevalence of mild or subclinical renal impairment in older patients or a preponderance of older subjects requiring invasive diagnostic and therapeutic studies; the latter is certainly the case with cardiac angiography and coronary angioplasty. Dehydration, a known risk factor in other causes of acute renal failure, is thought to play a role in approximately 41% of patients (Table 1). This finding calls for eliminating the routine practice of prohibiting oral fluids and of using preparatory purgation, especially in the older patient with either azotemia or diabetes. Other factors frequently encountered among patients with contrast-associated renal failure are hypertension, hyperuricemia (uric acid ≥ 8.0 mg/dl), and proteinuria (≥ +2 by dipstick), the latter being yet another marker for patients with intrinsic renal disease. Additional factors, such as large contrast loads (> 2 ml/kg) and repetitive contrast studies, as was the case in the present patient, have been incriminated as risk factors only in some studies and are worthy of more careful scrutiny in future investigations.

A review of risk factors would not be complete without mention of multiple myeloma. Early anecdotal reports suggested that patients with myeloma were at high risk for developing renal failure following the administration of contrast medium. Subsequent reviews including larger numbers of patients, however, have reported an aggregate incidence of less than 5% [42–44]. Additionally, several other factors commonly encountered in myeloma might predispose the patient to acute renal failure, including hypercalcemia, hyperuricemia, dehydration, nephrotoxic antibiotics, light-chain tubulopathy, and renal amyloidosis. In a study of 14 patients with myeloma and acute renal failure, only one episode appeared to be related to radiocontrast medium [42]. Given the numerous individual case reports, however, it would seem prudent to avoid the use of contrast agents whenever possible in patients with plasma cell dyscrasias.

I conclude that renal insufficiency per se predisposes to contrast-associated nephrotoxicity. The risk is clearly increased in patients with baseline serum creatinine levels of at least 1.5 mg/dl, and may even be increased in those with baseline levels between 1.1 and 1.5 mg/dl. Diabetes mellitus also is an important risk factor. The azotemic, proteinuric, diabetic patient, as exemplified by today's patient, clearly is at high risk for the development of acute renal failure following the administration of contrast medium. Contrast studies in such patients should be performed cautiously and only after alternative imaging techniques that entail less risk have been considered.

The clinical course of contrast-associated nephrotoxicity following diverse imaging techniques with a wide variety of contrast media has been well described [14, 45–47]. Although nonoliguric renal failure occurs in this setting, approximately two-thirds of reported cases have been oliguric; moreover, the oliguria generally is resistant to potent loop diuretics. I should emphasize that the true incidence of nonoliguric contrast-associated nephropathy is not known because systematic monitoring of renal function following contrast administration is not done routinely. The serum creatinine level usually begins to increase within the first 24 hours after administration of contrast media and peaks within 96 hours. Serum creatinine levels generally return to baseline values within 7 to 10 days, but renal failure requiring short-term or even chronic dialysis is a well-recognized outcome, particularly in patients whose baseline serum creatinine levels are greater than 4.0 mg/dl. In a study of 22 patients with advanced renal impairment who underwent high-dose excretory urography, a 25% decline in creatinine clearance, from 8.7 ml/min to 6.6 ml/min, was documented [48]. All patients experienced a decline in renal function, and 2 patients required chronic dialysis. In these two instances, renal angiography was performed following urography and before the creatinine clearance had returned to baseline. Data on 16 non-diabetic patients experiencing acute renal failure following intravenous pyelogram suggests that if the baseline serum creatinine is less than 4.0 mg/dl, the peak serum creatinine is not likely to exceed 8.0 mg/dl and that dialysis is usually not required [34]. On the other hand, if the baseline creatinine value is greater than 4.0 mg/dl, peak creatinine levels of greater than 8.0 mg/dl often are seen and dialysis is required more frequently. With baseline creatinine values of at least 8.0 mg/dl, renal failure commonly occurs.

Following the administration of contrast material, formed elements can appear in the urine, including renal tubular epithelial cells, casts, and debris. These findings are considered nonspecific and do not correlate with the development of renal functional alterations [49]. Urate crystals have been reported frequently and calcium oxalate crystals have been identified

Table 3. Possible pathogenetic factors

Hemodynamic alterations
Direct tubular toxicity
Intratubular obstruction
Microcirculatory changes
Immune mechanisms

occasionally [49]. Although heavy proteinuria has been described following contrast exposure [50], this finding is unusual.

In most patients with acute tubular necrosis, urine sodium excretion is greater than 40 mEq/liter, and fractional sodium excretion (FE_{Na}) exceeds 1%. Recent studies, however, have described paitents with acute renal failure with a low urinary sodium level and a low fractional excretion of sodium immediately following exposure to contrast medium. One-third of patients with renal failure who were tested after receiving contrast medium had a urinary sodium concentration of less than 20 mEq/liter [38]. Twelve consecutive patients with contrast-associated oliguric renal failure had a fractional excretion of sodium of less than 1.0% (range, 0.03% to 0.9%) [51]. This observation is not unique. A low fractional excretion of sodium, although usually associated with prerenal states or acute glomerulonephritis [52], has been described in at least one other variety of toxic nephropathy, that is, myoglobinuric acute renal failure [53]. Other studies, however, have failed to confirm the presence of a low fractional excretion of sodium in patients with contrast-associated nephropathy, so one must question the sensitivity of this finding [23].

Persistent visualization of the kidneys on plain radiography 24 to 48 hours after the administration of contrast medium has been thought to be characteristic of contrast nephropathy. In one study, this finding had a sensitivity of 83% and a specificity of 93% [54]. Other investigators, however, have described a high frequency both of false-positive and false-negative findings [14]. Clearly the most sensitive, specific, and cost-effective method of making the diagnosis of contrast-associated nephrotoxicity remains measurement of the serum creatinine level, obtained 24 to 48 hours following the administration of the contrast agent. I'll return to the critical importance of measurement of serum creatinine in my discussion of prevention.

The characteristic clinical syndrome of contrast-associated nephrotoxicity must be considered separate and distinct from the far less common but more catastrophic syndrome of renal failure due to cholesterol microemboli. This devastating phenomenon results not from contrast media but from vascular trauma induced by the catheters used during radiographic study and during angioplasty. The syndrome is typified by the insidious onset of renal failure following an intra-arterial contrast study. Renal failure usually progresses over several weeks and usually is irreversible. Diagnostic findings include livedo reticularis, elevated amylase levels, and peripheral eosinophilia [55]. The urine sediment is remarkably bland. Renal biopsy typically demonstrates pathognomonic microvascular cholesterol emboli.

Pathophysiology

Although several mechanisms have been suggested (Table 3), the precise pathogenesis of contrast-associated nephrotoxicity has not been elucidated. Observed features of the clinical

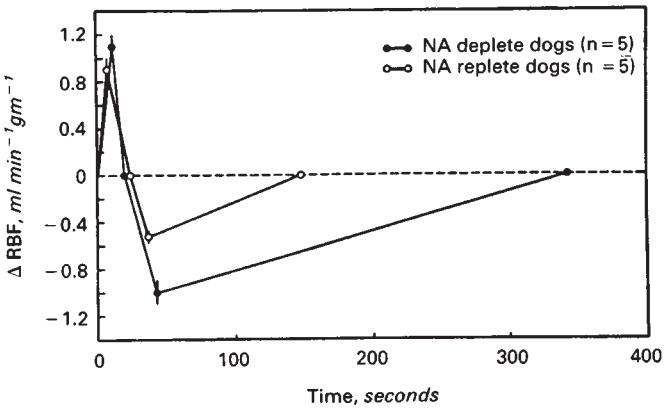

Fig. 1. *Renal blood flow response to injection of contrast medium in sodium-deplete and sodium-replete dogs plotted as the change in renal blood flow (ml/min^{-1} g^{-1} kidney weight) from baseline flow versus the time from the bolus injection of contrast medium.* (From Ref. 59.)

syndrome, including relatively rapid onset of oliguria, persistent nephrogram, low fractional excretion of sodium, and rapid resolution of renal failure, all support the notion that a reversible vasoconstrictor mechanism is operative. When contrast medium is injected directly into the renal artery, both renal blood flow and glomerular filtration rate abruptly decline [56–59]. This vasoconstrictor response, following a transient vasodilatory phase (Fig. 1), is unique to the renal vascular bed. The angiotensin II analogue Sarl-Ala8-AII decreases the duration but not the magnitude of the vasoconstriction; sodium repletion blunts both the magnitude and duration of the response [59]. Intracellular calcium appears to mediate the vasoconstrictor effect [60]. An infusion of either verapamil, diltiazem, or ethylene glycol-aminoethylether-tetracetic acid (EGTA) into the renal artery accentuates the contrast-induced initial vasodilatory phase while attenuating the vasoconstrictor phase; systemic hemodynamics are not altered. The role that these maneuvers might play in altering the development of contrast-associated nephrotoxicity is unknown, largely because a relevant animal model of contrast-induced renal failure was not available until recently.

Two experimental models have now been introduced and should help define the pathogenesis of this syndrome as well as identify useful protective measures. In New Zealand rabbits maintained for one week on a low-sodium diet, acute renal failure was consistently produced following administration of indomethacin (18 mg/kg), and an intravenous infusion of meglumine iothalamate (7 mg/kg). Glomerular filtration rate, as measured by endogenous creatinine clearance, significantly decreased within 24 hours and returned to baseline with 14 days. Two other groups of rabbits, receiving only contrast medium or indomethacin, did not experience a comparable decrement in glomerular filtration rate (Fig. 2) [61]. An acute infusion of either isotonic saline or isotonic mannitol, beginning one hour prior to contrast injection and continuing one hour after the injection, did not protect against the development of acute renal failure. However, animals given oral isotonic saline and daily subcutaneous injections of desoxycorticosterone acetate (DOCA, 1 mg/kg) did not develop acute renal failure following the administration of indomethacin and contrast medium. Light

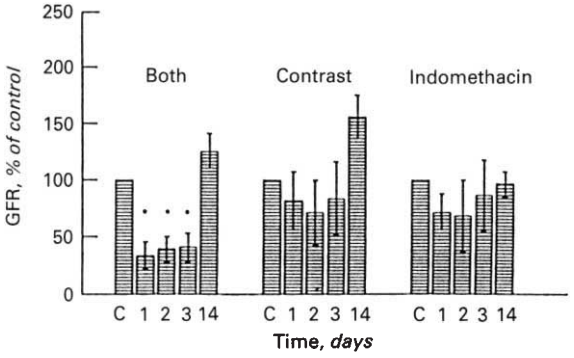

Fig. 2. *Glomerular filtration rate plotted as percentage of control (C) on days 1, 2, 3, and 14 following injection of contrast and indomethacin (N = 12), contrast alone (N = 10), or indomethacin alone (N = 9).* *Significant difference vs. C. (From Ref. 61.)

microscopy revealed no histologic alterations. Micropuncture studies disclosed a decrease in single-nephron filtration rate from 19.55 to 9.54 nl/min during acute renal failure with an increase to 17.73 nl/min two weeks later. Proximal tubular hydrostatic pressure and glomerular capillary pressure, as estimated by stop-flow pressure, were unchanged. Glomerular ultrafiltration coefficient (K_f) decreased from 1.28 ± 0.15 to 0.49 ± 0.10 nl/min/mm Hg following the induction of acute renal failure. No significant reduction in renal blood flow, as measured by electromagnetic flow probe, was observed during induction of acute renal failure. In this model, the reversible decrease in glomerular filtration induced by indomethacin and contrast media appeared to result from a reversible decrease in single-nephron filtration predicated upon a decrease in K_f, a decrease that could be prevented with one week of saline and DOCA but not with an acute infusion of saline or mannitol.

In another animal model [62], salt-depleted uninephrectomized Sabra rats received an acute infusion of indomethacin (10 mg/kg) and sodium iothalamate (6 ml/kg). Within 24 hours creatinine clearance fell significantly from 0.7 ± 0.1 to 0.2 ± 0.04 ml/min. This effect was not observed with administration of indomethacin or contrast medium alone. Histologic studies revealed necrosis of outer medullary thick ascending limbs (MTALs), tubular collapse, and casts. Specific cellular damage included mitrochondrial swelling, nuclear pyknosis, and cytoplasmic disruption with intracellular calcification. Areas most remote from oxygen supply, the deep outer medulla, manifested the most severe histologic damage. There was excellent correlation between the extent of MTAL injury and the increase in serum creatinine concentration. Additional findings included extensive proximal tubular (S_1S_2) vacuolization, as can be seen in humans [63]. The investigators speculated that the final pathway for contrast-induced renal injury in this model might be medullary hypoxia conditioned by medullary ischemia (due to volume depletion and prostaglandin inhibition) affecting metabolically active, hyperfiltering remnant nephrons.

Other studies, both pathologic and physiologic, support a role for direct tubular toxicity. Histologic alterations including proximal tubular vacuolar transformation, interstitial edema, and tubular degeneration have been reported [63, 64]. However, the significance of these findings is unknown because they do not uniformly correlate with renal dysfunction. Diatrizoate and iothalamate alter sodium transport in toad bladder [65]. In dogs [66, 67] and in humans [68], hyperosmolar injection of contrast medium into the renal artery is associated with a 30% to 50% decrease in PAH extraction (EPAH). Hyperosmolar control solutions cause no change in EPAH; the observed decrease in EPAH might be related to the tri-iodinated molecule. Enzymuria, including urinary alkaline phosphatase, LDH, SGOT, CPK, catalase, and glutathione transferase, has been seen both in dogs and humans following intra-arterial injection of hypertonic radiocontrast material, mannitol, and saline [69, 70]. Although release of these enzymes suggests cellular injury, enzyme release does not correlate with functional impairment.

Intratubular precipitation of both urinary protein and uric acid has been implicated in the pathogenesis of contrast-associated nephrotoxicity. Early reports of myeloma patients who sustained renal failure following administration of contrast medium implicated massive precipitation of Bence Jones protein with resultant tubular obstruction. Although currently employed agents might be less likely to cause precipitation of Bence Jones protein [71], these media have been associated with in-vitro precipitation of Tamm-Horsfall mucoprotein [72]. Whether such precipitation occurs in vivo is unknown. The uricosuric properties of contrast media are well known [72–74]. A 64% increase in urinary uric acid-to-creatinine ratio has been reported following arteriography in patients with underlying renal insufficiency. Only one patient has been reported with contrast nephropathy and pathologic changes compatible with acute urate nephropathy [15]. In one study, administration of allopurinol over 3 weeks prevented acute hyperuricosuria but did not prevent renal failure following exposure to contrast material [75]. In spite of the fact that urinary uric acid-to-creatinine ratios can exceed 1.0 following contrast administration, there is no compelling evidence that uricosuria represents a major mechanism for the development of contrast-associated nephrotoxicity.

Contrast agents are known to induce functionally significant changes in erythrocyte morphology and function, with subsequent microcirculatory sludging. Red blood cell crenation and spherocyte formation leading to erthyrocyte clumping and sludging with increased blood viscosity have been described in experimental animals [76–80]. Contrast medium infused directly into the renal artery of a dog is more toxic, as judged by histology, when given in blood than when given in saline; this finding suggests a role for microcirculatory compromise mediated by mechanical red blood cell changes [81]. Tri-iodinated contrast media cause a leftward shift of the oxyhemoglobin dissociation curve, both in patients and in vitro [82]. How these changes in red blood cell form and function relate to contrast-associated nephrotoxicity—if at all—remain unclear.

Severe allergic reactions to radiocontrast agents, including anaphylaxis and death, are well known. Infusion of contrast material in the rabbit leads to histamine release, a decrease in complement, and a fall in microarteriolar pressure [83]. In-vitro studies demonstrate serotonin release [84], platelet dysfunction [85], and formation of fibrin degradation products [86]. In one patient who developed renal failure following exposure to contrast material, IgM kappa antibodies against the contrast medium were detected [87]. Although patients can develop antibodies to contrast medium [87], the pathophysiologic significance of this finding remains unknown.

In summary, the available literature and recent insights from two new animal models suggest that contrast-associated nephrotoxicity is mediated by renal ischemia and resultant hypoxia combined with direct cellular toxicity of the iodinated molecule. Cellular toxicity is increased by both renal insufficiency and diabetic nephropathy, conditions associated with hyperfiltration of remnant nephrons and sclerosis of the renal vasculature. Conditions known to cause vasoconstriction and to interfere with autoregulation (for example, severe congestive heart failure, liver failure, volume depletion) could well aggravate the toxic effects.

Prevention

To date, attempts at preventing contrast-associated nephrotoxicity have been disappointing. Clearly, given that patients with elevated baseline serum creatinine levels are at high risk, avoiding or minimizing exposure to contrast material in such patients is prudent. Alternate imaging techniques such as ultrasonography, magnetic resonance imaging, nuclear imaging, or computerized axial tomography without contrast media should be considered. Efforts at avoiding preparatory volume depletion and minimizing contrast volume are rational. When repetitive contrast studies cannot be avoided, as with the patient who underwent coronary angioplasty following coronary angiography, serum creatinine values should be allowed to return to baseline following one study before one proceeds to the next.

Saline infusion has an appealing rationale in minimizing contrast-associated nephrotoxicity. In one report, success in preventing renal failure following angiography was attributed to the administration of 550 ml of normal saline per hour during the radiographic procedure [88].

Mannitol infusion also has been suggested as effective prophylaxis to prevent contrast-associated renal toxicity. Mannitol infusion prevents ischemic renal failure in the dog [89] and maintains GFR during controlled renal hypoperfusion in the rat [90]. An infusion of 500 ml of 5% mannitol prevented a contrast-induced decline in renal function in 6 patients with renal insufficiency (mean baseline creatinine, 2.51 mg/dl) [91]. A comparable group of 5 patients not receiving mannitol experienced a significant increase in serum creatinine, from 2.36 to 3.70 mg/dl, following exposure to a contrast agent. In the largest study reported to date, 37 patients, all with chronic renal insufficiency, were given 1500 ml of 0.45% sodium chloride, and then 250 ml of 20% mannitol within 60 minutes of the procedure [92]. In 8 patients (22%), serum creatinine increased significantly. The authors concluded that mannitol offered protection because a similar group of 40 unprotected patients experienced a 70% incidence of renal failure. A recent review recommended that all patients with a serum creatinine concentration of greater than 2.0 mg/dl be infused with 500 ml of 20% mannitol containing furosemide, 100 mg for each mg/dl of serum creatinine [93]. The authors recommended that this solution be infused at 20 ml/hr beginning one hour before and continuing for 6 hours after the procedure. They also recommended that urine output be replaced with 5% dextrose in water/0.45% sodium chloride containing 30 mEq of potassium chloride per liter. Unfortunately, no data were offered to support these recommendations.

Despite the absence of firm data, I along with many others routinely recommend preventive measures including hydration, minimization of contrast volume, spacing of procedures to allow the serum creatinine to return to its baseline level between exposures, and administration of furosemide and/or hypertonic mannitol. Table 4 contains the results of a survey I conducted of experienced nephrologists regarding their recommendations for prophylaxis of contrast-associated toxicity. A similar set of recommendations was endorsed in a recent editorial [94]. Unfortunately, as exemplified by the present patient, hydration and hypertonic mannitol often fail to prevent acute renal failure.

Table 4. Recommended prophylaxis[a]

Recommendation	Number recommending
Hydration	33
Minimize contrast volume	33
Space procedure: allow creatinine to return to baseline	33
Discontinue prostaglandin inhibitors	33
Hypertonic mannitol	26
Furosemide	26
Nonionic media	7
Sodium bicarbonate	5

[a] Results of an informal survey of 33 nephrologists, conducted in 1988 nationally.

Table 5. Properties of selected contrast agents

	Iodine *mg/dl*	Osmolarity *mOsm/liter*	Molecular wt *daltons*	$ Cost */g iodine*
Ionic agents				0.13–0.18
Hypaque (sodium diatrizoate)	300	1500	614	
Conray (meglumine iothalamate)	282	1217	614	
Renografin 60 (sodium/meglumine diatriazoate)	288	1511	614	
Conray 400 (sodium iothalamate)	400	1965	614	
Nonionic agents				2.43–3.06
Amipaque (metrizamide)	280	450	789	
Isovue (iopamidol)	300	616	777	
Amnipaque (iohexol)	300	620	821	

New contrast agents

The availability of newer iodinated contrast agents, nonionic monomers and dimers as well as ionic dimers, has raised the possibility of reducing or eliminating contrast-related toxicity. These agents are characterized by an increased number of iodine atoms per molecule (from 1.5 to 3.0 or 6.0), and thus have a markedly reduced osmolarity (Table 5). They are of comparable or improved diagnostic quality and appear to be associated with fewer side effects. Reductions in the incidence of local and systemic heat and pain, thrombophlebitis, nausea, vomiting, hypotension, reduced left ventricular contractile force, ventricular ectopy, and fibrillation have been reported [95, 96].

When injected directly into the real artery in an anesthetized

dog, a biphasic pattern of 10–20 seconds of vasodilation followed by a variable period of vasoconstriction is observed both with diatrizoate and iopamidol. Although pretreatment with buffered acetylsalicylic acid (10 mg/kg) lowered resting renal blood flow, it did not affect the previously observed contrast-induced biphasic fluctuation in renal blood flow, thereby suggesting that the acute hemodynamic alterations in renal blood flow induced by radiocontrast media are not mediated by prostaglandins [97]. Unfortunately, prostaglandin metabolites were not measured in this study.

In a second model using anesthetized dogs [98], in which 20 ml of either diatrizoate or iopamidol was injected directly into the renal artery, followed by complete balloon occlusion of the renal artery for 10 minutes, a significant decrease in average renal cortical blood flow (as measured by radioactive microsphere technique) was observed following infusion of a radiocontrast agent but not following a saline control. There was no difference between reductions in blood flow when diatrizoate was compared with iopamidol. Tubular or glomerular necrosis was seen in all animals receiving diatrizoate (6/6), in 4 of 6 receiving iopamidol, but also in 2 of 6 receiving a saline control; thus one can question the significance of the histologic changes observed.

Proximal tubular vacuolar transformation, so-called "osmotic nephrosis," has been observed following injection of diatrizoate, iopamidol, metrizamide, and ioxaglate [99]. These histologic changes, as I previously noted, do not correlate with renal dysfunction [63]. In a rabbit ear chamber model, metrizoate and metrizamide were associated with similar reductions in microcirculatory velocity [100]. In suspended rabbit proximal tubule segments [101], in which cellular injury was evaluated by alterations in intracellular potassium and calcium, by ATP depletion, and by basal respiratory rate, diatrizoate had greater cellular toxicity than did iopamidol. The toxicity was exacerbated by hypoxia.

Several clinical reports have concluded that these newer, nonionic agents are less nephrotoxic than are standard ionic monomers [102–109]. I think these studies are largely inconclusive, however, because they often have focused on patients with normal renal function, have not always included baseline creatinine values, and have not uniformly distinguished high-risk from low-risk individuals. In a recent study of 1144 patients who were given iopamidol during cardiac catheterization, a small but significant increase in basal serum creatinine levels was observed at both 24 and 48 hours after administration of the contrast agent [40]. An increment in serum creatinine of at least 0.5 mg/dl occurred in 65 patients (6%). As I mentioned previously, the probability of nephrotoxicity rose exponentially when the basal creatinine values exceeded 1.1 mg/dl. Another recent study, in which patients were randomly assigned to receive either ionic or nonionic contrast for cardiac angiography, found no significant difference in the incidence of contrast-associated nephrotoxicity [110].

We recently completed a prospective non-randomized study of 71 patients undergoing cardiac angiography with either ionic (diatrizoate) or nonionic (iopamidol) contrast medium [111]. All patients had baseline renal insufficiency, that is, a serum creatinine of at least 1.5 mg/dl. Risk factors, including renal impairment, diabetes, advanced age, and large contrast volume, were equally distributed between the two groups. All patients received 1000 ml of 0.45% sodium chloride prior to angiography. Renal failure was defined as an increase in serum creatinine of at least 1.0 mg/dl within 48 hours following administration of the contrast agent. The incidence of contrast-associated nephrotoxicity was 17% (6/36) in the patients receiving diatrizoate and 26% (9/35) in those receiving iopamidol ($P = 0.35$). One patient required short-term dialysis. Thus, the nephrotoxicity of nonionic contrast agents has been amply demonstrated. Moreover, the data suggest that these newer agents are not less nephrotoxic than are standard preparations, especially in the high-risk individual with renal impairment and/or diabetic nephropathy.

Due to the far greater cost of nonionic agents, the debate over their utilization has received national attention [112]. A recent report sponsored by the Rand Corporation estimates that nonionic contrast material, if employed routinely for all contrast studies, would represent an aggregate additional annual expense of $1 billion [113]!

Even more complex and unpredictable than cost considerations are the legal ramifications of using—or not using—the newer, nonionic media. At what point does failure to utilize a new technology deviate from ordinary medical practice? Does an appropriate standard of care include the routine use of nonionic media, or should only certain high-risk patients receive these agents? As responsible physicians, we must attempt to balance what is best for our patients with what is cost effective. From a nephrologic perspective, I do not think that the available data on the protective effect of nonionic contrast media are sufficiently strong to recommend the routine use of this expensive material, even in patients at high risk for developing contrast-associated nephrotoxicity.

Questions and answers

DR. ALAN KANTER (*Senior Attending Nephrologist, Michael Reese Hospital, Chicago, Illinois*): Is the rapid onset of brisk diuresis and the speedy recovery of renal function seen in today's patient described in the literature? Do we have an explanation for it?

DR. BERNS: Although the literature does describe the prompt resolution of contrast-induced renal failure in most patients, the brisk diuresis seen in the patient today is not specifically referred to. I can only speculate about the mechanism. Perhaps some of these patients undergo a diuresis during the recovery phase because of prior hydration and subsequent volume overload. Another possibility is excretion of the retained osmotically active contrast agents, as well as any mannitol that might have been used. This might have been the case with the patient presented today.

DR. JORDAN J. COHEN (*Dean of Medicine, State University of New York at Stony Brook, Stony Brook, New York*): How convincing is the evidence that contrast agents induce actual cytotoxicity within the tubular epithelium? An alternative explanation, of course, is that these agents induce hemodynamic changes and cause transient renal failure. Are there any in-vitro studies using tissue slices, cell suspensions, cell cultures, or the like that might shed light on whether contrast agents have direct cellular toxicity?

DR. BERNS: As I previously stated, certain indirect indicators of cellular damage, such as proximal tubular vacuolization and increase in urinary enzymes, do not correlate with functional

impairment. Toad bladder studies demonstrate contrast-related inhibition of active sodium transport and suggest a direct cellular effect independent of renal blood flow [65].

In a model of suspended rabbit proximal tubule cells [114], sodium diatrizoate was associated with alterations in tubule cell respiration, cation homeostasis, and adenine nucleotide metabolism. Under aerobic conditions, administration of 25 millimolar diatrizoate resulted in ATP depletion, an effect increased by 22.5 minutes of hypoxia. When a decrease in tubular potassium content or an increase in tubular calcium content was used as an index of cellular toxicity, radiographic contrast was shown to be toxic. Again, hypoxia increased this toxicity. I think these data suggest a role for direct cellular toxicity of radiographic agents. This toxicity probably can be increased by hypoxia or ischemia; thus a possible interaction exists between direct cellular factors and hemodynamic factors.

DR. SERAFINO GARELLA (*Acting Chairman of Medicine, Michael Reese Hospital*): The similarity between contrast-associated nephrotoxicity and that associated with nonsteroidal antiinflammatory agents is striking: the age distribution is the same; urinary sodium concentration is typically low; spontaneous recovery is the rule. This similarity prompts this question: is there any evidence that contrast agents inhibit prostaglandin production?

DR. BERNS: The relationship between contrast media and prostaglandins has been studied in female mongrel dogs [115]. Following an injection of meglumine iothalamate (2.5–3.3 ml/kg) into the lower thoracic aorta, both glomerular filtration rate (as measured by endogenous creatinine clearance) and renal blood flow (as calculated by gamma scintillation ^{131}I hippuran technique) decreased by approximately 20%. No significant changes in renal vein or aortic renin angiotensin II levels were observed. However, renal venous 6-keto-$PGF_{1\alpha}$, a prostacyclin metabolite, fell significantly; this change was observed at 35 minutes following the contrast injection. Calculated renal secretion rates for 6-keto-$PGF_{1\alpha}$ fell from a baseline value of 8 ng/min to 0 at 30 minutes and remained depressed as long as 100 minutes following contrast injection. The nadir in secretion of this prostaglandin metabolite corresponded to a period of reduction in renal blood flow and creatinine clearance. A causal relationship between the two has not been established, however. What role, if any, prostaglandin inhibition plays in clinical contrast-induced nephropathy is unknown. Based on these data as well as the observation that pharmacologic prostaglandin inhibition is a necessary component of the two animal models of contrast nephrotoxicity I discussed, I recommend that all drugs known to inhibit prostaglandin synthesis be discontinued prior to the administration of contrast material.

DR. NORMAN SIMON (*Director, Section of Nephrology, Evanston Hospital, Evanston, Illinois*): Many studies that have addressed the problem of contrast-associated nephropathy have defined renal failure as a rise in serum creatinine of at least 0.5 mg/dl; in some cases even a smaller number has been used. Other studies have used the definition that you employed, namely, a rise of at least 1.0 mg/dl. My question is whether these kinds of changes really reflect a clinically significant problem. In other words, if a patient's creatinine rises from 1.5 to 2.5 mg/dl and then falls back to 1.5 mg/dl, I would not consider that to indicate renal failure. What do you believe is a reasonable way to define this problem?

DR. BERNS: Certainly most patients with a 25% increase in the serum creatinine value are asymptomatic. However, if subsequent contrast studies are planned, I recommend that the creatinine be allowed to return to baseline prior to the administration of additional radiocontrast material. As in today's patient, the two episodes of renal failure added significantly to the overall hospital morbidity as well as to the duration and cost of the hospitalization. In our prospective study, the mean peak creatinine level among the 15 patients who developed renal failure was 4.65 ± .58 mg/dl; this value represents a clinically important degree of renal insufficiency. A conservative definition of contrast-induced acute renal failure is an increase in the serum creatinine of greater than or equal to 1.0 mg/dl within 48 hours following the administration of radiocontrast material.

DR. BRIAN DUFFY (*Attending Nephrologist, Michael Reese Hospital*): If the clinical circumstances require a contrast study, what do you recommend for patients with moderately severe renal failure, say, those with a serum creatinine greater than 5 mg/dl?

DR. BERNS: By all accounts, you are describing a high-risk patient. Whenever possible, I recommend avoiding contrast studies at this level of renal impairment. When such studies cannot be avoided, however, as is frequently the case with major arteriography, I recommend that any nonsteroidal antiinflammatory agents be stopped well in advance of the study. Furthermore, I recommend aggressive intravenous hydration, except, of course, where congestive heart failure exists. I combine intravenous hydration with the administration of 12.5 to 25.0 g of hypertonic mannitol immediately prior to the contrast study. When volume overload is a concern, intravenous furosemide can be given either immediately before or immediately after the contrast agent is administered. Post-contrast volume depletion can be avoided by routine monitoring of urinary output and by intravenous fluid replacement as required. Another potentially useful strategy is minimizing contrast volume whenever feasible. For example, in patients undergoing cardiac angiography, a left ventriculogram frequently can be avoided and comparable information obtained with a multigated nuclear study. Unfortunately, I have no data generated from randomized, prospective studies to support these recommendations. I have only clinical experience and impressions to guide me.

DR. COHEN: What is the frequency with which permanent renal damage follows exposure to contrast agents? Does such damage occur in nondiabetics as well as in diabetic patients?

DR. BERNS: Permanent renal damage has been documented in diabetic and nondiabetic patients [29, 34, 48]. Fortunately, it appears to be a relatively unusual complication cited infrequently in the literature. Much of the clinical literature is characterized by a lack of long-term followup; therefore, the incidence of permanent renal impairment is not known with certainty. In this regard, Schwartz and colleagues recommended in 1963 that urography be avoided completely in patients with advanced renal failure whose creatinine level was greater than 10 mg/dl [9]. My own experience is that in the vast majority of patients, creatinine does return to baseline values, but that in patients whose baseline creatinine values exceed 8 mg/dl, contrast administration carries a high risk for induction of permanent renal failure requiring dialysis.

DR. COHEN: One feature of this condition seems to be agreed

on by everyone: if some degree of renal insufficiency is already present, the risk of contrast-associated nephropathy is substantially greater than if renal function is normal to start with. How do you explain this observation? Why are these patients, even those with mild degrees of renal insufficiency, so much more susceptible?

DR. BERNS: I am not sure that we have a definite explanation for this observation. Perhaps the patient with a diminished nephron mass experiences a greater load of contrast per functioning nephron with subsequent increased cellular toxicity. An alternate explanation might involve the presence of underlying vascular disease in patients with renal parenchymal damage and subsequent blunting or loss of autoregulation. This would render the kidney that much more susceptible to any hemodynamic insult, no matter how transient. This also could explain the apparent exacerbation of nephrotoxicity in patients with congestive heart failure, liver failure, and volume depletion, all conditions known to be associated with compromised renal autoregulation.

DR. STUART SPRAGUE (*Renal Fellow, University of Chicago/Michael Reese Hospital*): Patients with severe renal failure, and even those receiving dialysis, occasionally require a contrast study. Is it necessary to institute dialysis immediately after such a study to remove the contrast material from the body?

DR. BERNS: I know of no studies that help us answer this question. After contrast medium enters the circulation, it distributes in the extracellular fluid compartment and does not undergo significant metabolism or biotransformation. The major route of excretion is, of course, renal. Therefore one would anticipate significant retention of contrast medium in the dialysis patient. As a non-protein-bound molecule of middle molecular weight, iodinated contrast material should be removed by dialysis. The vast majority of dialysis patients tolerate the retained contrast without apparent complication. Only when volume overload and pulmonary edema develop do we recommend immediate dialysis following a contrast procedure. We routinely schedule contrast procedures on nondialysis days. In well-dialyzed patients, I rarely have had to perform emergency dialysis to remove the administered contrast agent.

DR. COHEN: You noted that the risk of contrast-associated nephropathy in diabetic patients with moderate renal insufficiency is roughly proportional to the serum creatinine level. Is the same true in nondiabetic patients?

DR. BERNS: I believe so; however, the literature has not carefully divided patients with widely varying serum creatinine levels into groups. My own experience indicates that as the baseline creatinine rises, so does the risk for both the diabetic and nondiabetic patient.

DR. SIMON: I am intrigued by the observation that only the kidney appears to manifest contrast-induced vasoconstriction. Does the vasoconstriction depend on the site of injection?

DR. BERNS: The intravascular administration of radiographic contrast material is associated with vasodilation in most vascular beds. The unique biphasic response of the renal vascular bed is seen only following injection of contrast material directly into the renal artery.

DR. KAI LAU (*Director, Division of Nephrology, Michael Reese Hospital*): If one used a more sensitive measure of glomerular filtration rate than serum creatinine—for example, inulin clearance—and measured GFR systematically before and after contrast studies in patients with normal renal function, might one also detect a fall in filtration rate even though serum creatinine levels might not appear to change?

DR. BERNS: Perhaps a more sensitive measurement of GFR would detect subtle decrements in GFR in a greater percentage of patients. Certainly measuring the serum creatinine 24 hours after a contrast study has its limitations; however, studies on 38 normal individuals using 2-hour creatinine clearance levels before and immediately after angiography did not demonstrate a measurable decrement in glomerular filtration rate [49].

Reprint requests to Dr. A. Berns, 55 East Washington, Suite 1100, Chicago, Illinois 60602, USA

References

1. HOU SH, BUSHINSKY DA, WISH JB, COHEN JJ, HARRINGTON JT: Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 74:243–248, 1983
2. PENDERGRASS EP, HODES PJ, TRONDREAU RJ, POWELL CC, BURDICK ED: Further consideration of deaths and unfavorable sequelae following administration of contrast media in urography in the United States. *Am J Roentgenol* 74:262–287, 1955
3. FISCHERMANN K, OSTENFELD J: Death following intravenous urography. *Nord Med* 45:240, 1951
4. MILLER GM, WILIE EJ, HINMAN F: Renal complications from aortography. *Surgery* 35:885, 1954
5. LARSSON H, PALMLOV A: Abdominal aortography with special reference to its complications. *Acta Radiol* 38:111, 1954
6. BARNES BA, SHAW AS, LEAF A, LINTON RR: Oliguria following diagnostic translumbar aortography. *N Engl J Med* 252:113, 1955
7. EDLING NPG, EDVALL CA, HELANDER CG: On renal damage due to aortography and its prevention by renal tests. *Acta Radiol* 47:473, 1957
8. MACEWAN DW, DUNBAR JS: Intravenous pyelography in children with renal insufficiency. *Radiology* 78:893, 1962
9. SCHWARTZ WB, HURWIT A, ETTINGER A: Intravenous urography in the patient with renal insufficiency. *N Engl J Med* 269:277–283, 1963
10. STARK FR, COBURN JW: Renal failure following methylglucamine diatrizoate (Renografin) aortography. Report of a case with unilateral renal artery stenosis. *J Urol* 96:845, 1966
11. BERGMAN AL, ELLISON MR, DUNEA G: Acute renal failure after drip infusion pyelography. *N Engl J Med* 279:1277, 1978
12. WAGONER RD: Acute renal failure associated with contrast agents (*editorial*). *Arch Intern Med* 138:353, 1978
13. HENEGHAN M: Contrast induced acute renal failure (*editorial*). *Am J Roentgenol* 131:1113, 1978
14. BYRD L, SHERMAN RL: Radiocontrast-induced acute renal failure. A clinical and pathophysiologic review. *Medicine* 58:270–279, 1979
15. HARKONEN S, KJELLSTRAND C: Contrast nephropathy. *Am J Nephrol* 7:69–77, 1981
16. DIAZ-BUXO JA, WAGONER RD, HATTERY RR, PALUMBO PJ: Acute renal failure after excretory urography in diabetic patients. *Ann Intern Med* 83:155–158, 1975
17. PORT KF, WAGONER RD, FULTON RE: Acute renal failure after angiography. *Am J Roentgenol* 121:544–550, 1974
18. KRUMLOVSKY FA, SIMON N, SANTHANAM S, DELGRECO F, ROXE D, POMARANC MM: Acute renal failure: association with administration of radiographic contrast material. *JAMA* 239:125–127, 1978
19. KUMAR S, HULL JD, LATHI S, COHEN AJ, PLETKA PG: Low incidence of renal failure after angiography. *Arch Intern Med* 141:1268–1270, 1981
20. D'ELIA JA, GLEASON RE, ARDAY M, MALARICK C, GODFREY K, WARRAN J, KALDANY A, WEINRAUCH LA: Nephrotoxicity from angiographic contrast material. A prospective study. *Am J Med* 72:719–725, 1982

21. MASON RA, ARBEIT LA, GIRON F: Renal dysfunction after arteriography. *JAMA* 253:1001–1004, 1985
22. TERUEL JL, MARCER R, ONAINDIA JM, SERANO A, QUEREDA C, ORTUNO J: Renal function impairment caused by intravenous urography. *Arch Intern Med* 141:1271–1274, 1981
23. SHAFI T, SHYAN-YIK C, PORUSH JG, SHAPIRO WB: Infusion intravenous pyelography and renal function. Effects in patients with chronic renal insufficiency. *Arch Intern Med* 138:1218–1221, 1978
24. EISENBERG RL, BANK WO, HEDGCOCK MW: Renal failure after major angiography. *Am J Med* 68:43–46, 1980
25. COCHRAN ST, WONG WS, ROE DJ: Predicting angiography induced acute renal function impairment: clinical risk model. *Am J Roentgenol* 14:1027–1033, 1983
26. BARRETT BJ, PARFREY DS, GRIFFITHS SM, WITHERS J, PAUL MD, MCMANAMON PJ: Contrast nephropathy in subjects with preexisting renal failure: A prospective controlled study (*abstract*). *Proc Am Soc Nephrol* 1987, p33A
27. SHIEH SD, HIRSCH HR, BOSHELL BR, PINO JA, ALEXANDER LJ, WITTER DM, FRIEDMAN EA: Low risk of contrast media-induced acute renal failure in nonazotemic type-2 diabetes mellitus. *Kidney Int* 21:739–743, 1982
28. WEINRAUCH LA, HEALY RW, LELAND OS, GOLDSTEIN HH, KASSISSIEH SD, LIBERTINO JA, TAKACS FJ, D'ELIA JA: Coronary angiography and acute renal failure in azotemic diabetic nephropathy. *Ann Intern Med* 86:56–59, 1977
29. TALIERCIO CP, VLIETSTRA RE, FISHER LD, BURNETT JC: Risks for renal dysfunction with coronary angiography. *Ann Intern Med* 104:501–504, 1986
30. SWARTZ RD, RUBIN JE, LEEMING BW, SILVA P: Renal failure following major angiography. *Am J Med* 65:31–37, 1978
31. HARKONEN S, KJELLSTRAND CM: Intravenous pyelography in nonuremic diabetic patients. *Nephron* 24:268–270, 1979
32. HARKONEN S, KJELLSTRAND CM: Exacerbation of diabetic renal failure following intravenous pyelography. *Am J Med* 63:939–946, 1977
33. STAGE P, BRIX E, FOLKE K, KARIE A: Urography in renal failure. *Acta Radiol [Diagn]* (Stockh) 11:337–345, 1970
34. VAN ZEE BE, HOY WE, TALLEY TE, JAENIKE JR: Renal injury associated with intravenous pyelography in nondiabetic and diabetic patients. *Ann Intern Med* 89:51–54, 1978
35. PARFREY PS, GRIFFITHS SM, BARRETT BJ, PAUL DM, GENGE M, WITHERS J, FARID N, MCMANOMON P: Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. *N Engl J Med* 320:143–149, 1989
36. ALEXANDER RD, BERKES SL, ABUELO G: Contrast media induced oliguric renal failure. *Arch Intern Med* 138:381–384, 1978
37. ANSARI Z, BALDWIN DS: Acute renal failure due to radiocontrast agents. *Nephron* 17:28–40, 1976
38. CARVALLO A, RAKOWSKI TA, ARGY WP, SCHRIENER GE: Acute renal failure following drip infusion pyelography. *Am J Med* 65:38–45, 1975
39. KAMDAR A, WEIDMAN P, MAKOFF DL, MASSRY SG: Acute renal failure following intravenous use of radiographic contrast dyes in patients with diabetes mellitus. *Diabetes* 26:643–649, 1977
40. DAVIDSON CJ, HLATKY M, MORRIS KG, PIEPER K, SKELTON TN, SCHWAB SJ, BASHORE TM: Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. *Ann Intern Med* 110:119–124, 1989
41. PILLAY VK, ROBBINS PC, SCHWARTZ FD, KARK RK: Acute renal failure following intravenous urography in patients with long-standing diabetes mellitus and azotemia. *Radiology* 95:633–636, 1970
42. DEFRONZO RA, HUMPHREY RL, WRIGHT JR, COOKE CR: Acute renal failure in multiple myeloma. *Medicine* 54:209, 1975
43. MYERS GH, WITTER DM: Acute renal failure after excretory urography in multiple myeloma. *Am J Roentgenol* 113:583, 1971
44. VIX VA: Intravenous pyelography in multiple myeloma. Review of 52 studies in 40 patients. *Radiology* 87:896, 1966
45. CRONIN RE: Radiocontrast media-induced acute renal failure, in *Diseases of the Kidney* (4th ed), edited by SCHRIER RW, GOTTSCHALK CW, Boston, Little, Brown, 1987, pp 1301–1317
46. COGGINS CH, FANG LST: Acute renal failure associated with antibiotics, anesthetic agents and radiographic contrast agents, in *Acute Renal Failure* (2nd ed), edited by BRENNER B, LAZARUS M, Philadelphia, Saunders, 1988, pp 295–352
47. MISSION RT, CUTLER RE: Radiocontrast-induced renal failure. *West J Med* 142:657–664, 1985
48. MILLMAN N, GOTTLIEB P: Renal function after high dose urography in patients with chronic renal insufficiency. *Clin Nephrol* 7:250–254, 1977
49. GELMAN ML, ROWE JW, COGGINS CH, ATHANASOULIS C: Effects of an angiographic contrast agent on renal function. *Cardiovasc Med* 4:313–320, 1979
50. TEJLER L, ALMEN T, HOLTAS S: Proteinuria following nephroangiography. *Acta Radiol [Diagn]* 18:634–640, 1977
51. FANG LST, SIROTA RA, EBERT TH, LICHENSTEIN NS: Low fractional excretion of sodium with contrast media induced acute renal failure. *Arch Intern Med* 140:531–533, 1980
52. MILLER TR, ANDERSON RJ, LINAS S, HENRICH W, BERNS A, GABOW P, SCHRIER RW: Urinary diagnostic indices in acute renal failure. A prospective study. *Ann Intern Med* 88:47–50, 1978
53. STEINER RW: Low fractional excretion of sodium in myoglobinuric renal failure. *Arch Intern Med* 142:1216–1217, 1982
54. OLDER RA, KOROBKIN M, CLEEVE DM, SCHAAF R, THOMPSON W: Contrast induced acute renal failure: persistent nephrogram as clue to early detection. *Am J Roentgenol* 134:339–342, 1980
55. KASINATH BS, CORWIN HL, BINDANI AK, KORBET SM, SCHWARTZ MM: Eosinophilia in the diagnosis of atheroembolic renal disease. *Am J Nephrol* 7:173–177, 1987
56. CALDICOTT W, HOLLENBERG NK, ABRAMS HL: Characteristics of response of renal vascular bed to contrast media. *Invest Radiol* 5:539–547, 1970
57. SHERWOOD T, LAVENDER JD: Does renal blood flow rise or fall in response to diatrizoate? *Invest Radiol* 4:327–328, 1969
58. TALNER LB, DAVIDSON AJ: Renal hemodynamic effects of contrast media. *Invest Radiol* 3:310, 317, 1968
59. LARSON TS, HUDSON K, MERTZ JI, ROMERO JC, KNOX FG: Renal vasoconstriction response to contrast media. The role of sodium balance and the renin-angiotensin system. *J Lab Clin Med* 101:385–391, 1983
60. BAKRIS GL, BURNETT JC: A role for calcium in radiocontrast-induced reductions in renal hemodynamics. *Kidney Int* 27:465–468, 1985
61. VARI RC, NATARAJAN LA, WHITESCARVER SA, JACKSON BA, OH CE: Induction, prevention and mechanisms of contrast media-induced acute renal failure. *Kidney Int* 33:699–707, 1987
62. HEYMAN SN, BREZIS M, REUBINOFF CA, GREENFIELD C, LECHENE FH, EPSTEIN FH, ROSEN S: Acute renal failure with selective medullary injury in the rat. *J Clin Invest* 82:401–412, 1988
63. MOREAU JF, DROZ D, SABTO J, JUNGERS P, KLEINKNECHT D, HINGLAIS N, MICHEL JR: Osmotic nephrosis induced by water-soluble triiodinated contrast media in man. *Radiology* 115:329–336, 1975
64. MOREAU JF, DROZ D, NOEL LH: Nephrotoxicity of metrizamide in man (*letter*). *Lancet* 1:1201, 1978
65. ZIEGLER TW, LUDENS JH, FANESTIL D: Inhibition of active sodium transport by radiographic contrast media. *Kidney Int* 7:68–73, 1975
66. DANFORD RO, TALNER LB, DAVIDSON AJ: Effect of graded osmolalities of saline solution and contrast media on renal extraction of PAH in the dog. *Invest Radiol* 4:301–304, 1969
67. NORBY LH, DIBONA GF: The renal vascular effects of meglumine diatrizoate. *J Pharm Exp Ther* 193:923–927, 1975
68. SORBY WA, HOY RJ: Renal arteriography and renal function. *Australas Radiol* 12:252–256, 1968
69. HARTMANN HG, BRAEDEL HE, JUTZLER GA: Detection of renal tubular lesions after abdominal aortography and selective arteriography by quantitative measurement of brush-border enzymes in the urine. *Nephron* 39:95–101, 1985
70. GOLDSTEIN EJ, FEINFELD DA, FLEISCHNER GM, ELKIN M: Enzymatic evidence of renal tubular damage following renal angiography. *Radiology* 121:617–621, 1976
71. CWYNARSKE MT, SAXTON HM: Urography in myelomatosis. *Br Med J* 1:486–487, 1969
72. BERDON WE, SCHWARTZ RH, BECKER J, BAKER DH: Tamm

Horsfall proteinuria: Its relationship to prolonged nephrogram in infants and children and to acute renal failure following intravenous urography in adults with multiple myeloma. *Radiology* 92:714–718, 1969
73. MUDGE GH: Uricosuric action of cholangiographic agents: a possible factor in nephrotoxicity. *N Engl J Med* 284:929, 1971
74. POSTLETHWAITE AE, KELLEY WN: Uricosuric effect of radiocontrast agents: study in man of four commonly used preparations. *Ann Intern Med* 74:845, 1971
75. FELDMAN MA, GOLDFARB S, MCCURDY DK: Recurrent radiography dye-induced acute renal failure. *JAMA* 229:72, 1974
76. READ RC, MEYER M: Role of red cell agglutination in arteriographic complications. *Surg Forum* 10:472–475, 1959
77. GARBER GL, READ RC: Red cell factor in renal damage from hypertonic solutions. *Proc Soc Exp Biol Med* 107:165–169, 1961
78. SORBIN SS, FASHER WG, JACOBSON G, VANEECKHAVEN FA: Nature of adverse reactions to radiopaque agents. *JAMA* 170: 1546–1547, 1959
79. DERRICK JR, BROWN RW, LIVANEC G: Experimental effects of arteriography on microcirculation. *Am J Surg* 116:712–717, 1970
80. SCHIANTARELLI P, PERONI F, ROSATI G: Effects of iodinated contrast media on erythrocytes. *Invest Radiol* 8:199, 1973
81. DEAN RE, ANDREW JH, RAD R: The red cell factor in renal damage from angiographic media. *JAMA* 187:27–31, 1964
82. ROSENTHAL L, LITWAN SB, LAVER MB: Effects of contrast media used in angiography on hemoglobin-oxygen equilibrium. *Invest Radiol* 8:191–198, 1973
83. RING J, ENDRICH B, INTAGLIETTA M: Histamine release, complement consumption and microvascular changes after radiographic contrast media infusion in rabbits. *J Lab Clin Med* 92: 584–594, 1978
84. RING J, ARROYAVE CM, FRITZLER MJ, TAN EM: *In vitro* histamine and seratonin release by radiographic contrast media. Complement dependent and independent release reaction and changes in ultrastructure of human blood cells. *Clin Exp Immunol* 32:105, 1978
85. BRASCH RC, CALDWELL JL: The allergic theory of radiocontrast agent nephrotoxicity. *Invest Radiol* 11:347–356, 1976
86. SIMON RA, SCHATZ M, STEVENSON DD, CURRY N, YAMAMOTO F, PLOW E, RING J, ARROYAVE CM: Radiographic contrast media infusions: measurement of mediators and correlations with clinical parameters. *J Allergy Clin Immunol* 6:145–153, 1978
87. KLEINKNECHT D, DELOUX J, HOMBERG JC: Acute renal failure after intravenous urography. Detection of antibodies against contrast media. *Clin Nephrol* 2:116–119, 1974
88. EISENBERG RL, BANK WO, HEDGCOCK MW: Renal failure after major angiography can be avoided with hydration. *Am J Roentgenol* 136:859–861, 1981
89. CRONIN RE, ERICKSON AB, DETORRENTE A, MCDONALD KM, SCHRIER RW: Norepinephrine-induced acute renal failure: A reversible ischemic model of acute renal failure. *Kidney Int* 14:187–193, 1978
90. MORRIS CR, ALEXANDER EA, BRUNS F, LEVINSKY N: Restoration and maintenance of glomerular filtration by mannitol during hypoperfusion of the kidney. *J Clin Invest* 51:1555–1564, 1972
91. OLD CW, LEHRNER LM: Prevention of radiocontrast induced acute renal failure with mannitol (*letter*). *Lancet* 1:885, 1980
92. ANTO HR, CHOU SY, PORUSH JG, SHAPIRO WB: Infusion intravenous pyelography and renal function: effects of hypertonic mannitol in patients with chronic renal insufficiency. *Arch Intern Med* 141:1652–1656, 1981
93. BERKSETH RO, KJELLSTRAND CM: Radiologic contrast induced nephropathy. *Med Clin North Am* 68:351–371, 1984
94. BREZIS M, EPSTEIN FH: A closer look at radiocontrast-induced nephropathy. *N Engl J Med* 320:179–181, 1989
95. SPATARO RF: Newer contrast agents for urography. *Radiol Clin North Am* 22:365–381, 1984
96. BETTMAN MA, MORRIS TW: Recent advances in contrast agents. *Radiol Clin North Am* 24:347–357, 1986
97. LUND G, EINZIG S, RYSAVY J, SALOMONOWITZ E, CASTANEDA-ZUNIGA W, AMPLATZ K: Effect of prostaglandin inhibition on the renal vascular response to ionic and non-ionic contrast media in the dog. *Acta Radiol Diag* 25:407–410, 1984
98. LUND G, EINZIG S, RYSAVY J, BORGWARDT B, SALOMONOWITZ E, CRAGG A, AMPLATZ K: Role of ischemia in contrast-induced renal damage. *Circulation* 69:783–789, 1984
99. MOREAU JF, DROZ D, NOEL LH, LEIBOWITCH J, JUNGERS P, MICHEL JR: Tubular nephrotoxicity of water-soluble iodinated contrast media. *Invest Radiol* 15:554–560, 1980
100. EKELAND A, UFLACKER R: Effect of meglumine metrizoate and metrizamide on the microcirculation. *Acta Radiol [Diagn]* 19: 969–976, 1978
101. HUMES DS, CIESLINSKI DA, MESSANA JM: Pathogenesis of radiocontrast-induced acute renal failure: Comparative nephrotoxicity of diatrizoate and iopamidol. *Diagn Imag (suppl)* vol 9, May 12–18, 1987
102. KHOURY GA, HOPPER JC, VARGHESE Z, FARRIGTON K, DICK R, IRVING JD, SWENY P, FERNANDO OM, MOORHEAD JF: Nephrotoxicity of ionic and nonionic contrast material in digital vascular imaging and selective renal arteriography. *Br J Radiol* 56:631–635, 1983
103. LEVORSTAD K, KOLBENSTVEDT A, LOYNING EW: Iohexol compared with metrizoate in urography. *Acta Radiol [Diagn]* 24: 337–342, 1983
104. GALE ME, ROBBINS AH, HARBURGER RJ: Renal toxicity of contrast agents: iopamidol, iothalamate and diatrizoate. *Am J Radiol* 142:333–335, 1984
105. TORNQUIST C, HOLTAS S: Renal angiography with iohexol and metrizoate. *Radiology* 150:331–334, 1984
106. SCHIAVINA G, ARRIGO G, VERGNAGHI D: Nephrotoxicity of contrast media: Comparison of iopamidol and diatrizoate by measurement of urinary enzymes after urography. *Radiol Med* (Torino) 70:176–179, 1984
107. BANI E, FEDERIGHI F, GHIO R: The use of iohexol in pediatric urography. A comparative study with meglumine diatrizoate. *Int J Pediatr Nephrol* 6:271–274, 1985
108. SMITH HJ, LEVORSTAD K, BERG KH: High dose urography in patients with renal failure: a double blind investigation of iohexol and metrizoate. *Acta Radiol* [Diagn] 26:213–220, 1985
109. HOLTAS S, ALVER T, HELLSTEN S: Proteinuria following nephroangiography: VI. Comparison between metrizoate and metrazamide in man. *Acta Radiol* [Diagn] 21:491–494, 1980
110. SCHWAB SJ, HLTAKY MA, PIEPER KS, DAVIDSON CJ, MORRIS KG, SKELTON TN, BASHORE TM: Contrast nephrotoxicity: A randomized controlled trial of a nonionic and an ionic radiographic contrast agent. *N Engl J Med* 320:149–153, 1989
111. NORA N, BERNS A: Renal failure following cardiac angiography: a prospective study of diatrizoate and iopamidol (*abstract*). *Kidney Int* 35:414, 1989
112. "Can You Afford to Get Sick?" *Newsweek*, 30 Jan 1989, pp 44–49
113. JACOBSON PD, ROSENQUIST CJ: The introduction of low-osmolar contrast agents in radiology: medical, economic, legal and public policy issues. *JAMA* 260:1586–1592, 1988
114. HUMES HD, HUNT DA, WHITE MD: Direct toxic effect of the radiocontrast agent diatrizoate on renal proximal tubule cells. *Am J Physiol* (Renal Fluid Electrolyte Physiol) 252:F246–F255, 1987
115. WORKMAN RJ, SHAFF MI, JACKSON RV, DIGGS J, FRAZER MG, BRISCOE C: Relationship of renal hemodynamic and functional changes following intravascular contrast to the renin-angiotensin system and renal prostacyclin in the dog. *Invest Radiol* 18: 160–166, 1983